Mesenchymal Stem Cells Reduce Corneal Fibrosis and Inflammation via Extracellular Vesicle-Mediated Delivery of miRNA.

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Public Summary:
Mesenchymal stem cells from corneal stromal stem cells (CSSC) prevent fibrotic scarring and stimulate regeneration of transparent stromal tissue after corneal wounding in mice. These effects rely on the ability of CSSC to block neutrophil infiltration into the damaged cornea. The current study investigated the hypothesis that tissue regeneration by CSSC is mediated by secreted extracellular vesicles (EVs). CSSC produced EVs 130-150 nm in diameter with surface proteins that include CD63, CD81, and CD9. EVs from CSSC reduced visual scarring in murine corneal wounds as effectively as did live cells, but EVs from human embryonic kidney (HEK)293T cells had no regenerative properties. CSSC EV treatment of wounds decreased expression of fibrotic genes Col3a1 and Acta2, blocked neutrophil infiltration, and restored normal tissue morphology. CSSC EVs labeled with carboxyfluorescein succinimidyl ester dye, rapidly fused with corneal epithelial and stromal cells in culture, transferring microRNA (miRNA) to the target cells. Knockdown of mRNA for Alix, a component of the endosomal sorting complex required for transport, using siRNA, resulted in an 85% reduction of miRNA in the secreted EVs. The EVs with reduced miRNA were ineffective at blocking corneal scarring. Furthermore, CSSC with reduced Alix expression also lost their regenerative function, suggesting EVs as an obligate component in the delivery of miRNA. The results of these studies support an essential role for extracellular vesicles in the process by which CSSC cells block scarring and initiate regeneration of transparent corneal tissue after wounding. EVs appear to serve as a delivery vehicle for miRNA, which affects the regenerative action. Stem Cells Translational Medicine 2019;8:1192-1201.

Scientific Abstract:
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